Lamivudine (3TC/Epivir)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Oral Solution: 10 mg/mL (Epivir); 5 mg/mL (Epivir HBV*)

Tablets: 150 mg (scored) and 300 mg (Epivir); 100 mg (Epivir HBV*)

Combination Tablets:

- *With zidovudine (ZDV):* 3TC 150 mg + ZDV 300 mg (Combivir)
- *With abacavir (ABC):* 3TC 300 mg + ABC 600 mg (Epzicom)
- *With ZDV and ABC:* 3TC 150 mg + ZDV 300 mg + ABC 300 mg (Trizivir)

* *Epivir HBV oral solution and tablets contain a lower amount of 3TC than Epivir oral solution and tablets. The formulation and dosing of 3TC in Epivir HBV was maximized for the treatment of hepatitis B virus (HBV) only. If Epivir HBV is used in HIV-infected patients, the higher dosage indicated for HIV therapy should be used as part of an appropriate combination regimen. The Epivir HBV tablet is appropriate for use in children who require a 100-mg 3TC dose for treatment of HIV infection.*

Dosing Recommendations

Epivir (oral solution and tablets)

Neonate/infant dose (age <4 weeks) for prevention of transmission or treatment:
2 mg/kg twice daily.

Pediatric dose (age ≥4 weeks):
4 mg/kg (maximum dose 150 mg) twice daily.

Pediatric dosing for scored 150-mg tablet (body weight ≥14 kg):

Weight (kg)	AM dose	PM dose	Total Daily Dose (mg)
14–21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21 to <30	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥30	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

Adolescent (age ≥16 years)/adult dose:
Body weight <50 kg:
4 mg/kg (up to 150 mg) twice daily.
Body weight ≥50 kg:
150 mg twice daily or 300 mg once daily.

Selected Adverse Events

- Minimal toxicity
- Exacerbation of hepatitis has been reported after discontinuation of 3TC in the setting of chronic hepatitis B infection.

Special Instructions

- 3TC can be given without regard to food.
- Store 3TC oral solution at room temperature.
- Screen patients for HBV infection before administering 3TC.

Metabolism

- Renal excretion—dosage adjustment required in renal insufficiency.
  - Combivir and Trizivir (fixed-dose combination products) should not be used in patients with creatinine clearance (CrCl) <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Combivir
Adolescent (body weight ≥30 kg)/adult dose:
1 tablet twice daily.

Trizivir
Adolescent (body weight >40 kg)/adult dose:
1 tablet twice daily.

Epzicom
Adolescent (age >16 years and body weight >50 kg)/adult dose:
1 tablet once daily.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- *Renal elimination:* Drugs that decrease renal function could decrease clearance of lamivudine.
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Do not use lamivudine in combination with emtricitabine because of the similar resistance profiles and no additive benefit[1].

Major Toxicities:

- *More common:* Headache, nausea.
- *Less common (more severe):* Peripheral neuropathy, pancreatitis, lipodystrophy/lipoatrophy.
- *Rare:* Increased liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/3TC.html).

Pediatric Use: Lamivudine is Food and Drug Administration (FDA) approved for use in children from birth onward, and it is a common component of most nucleoside backbone regimens.

Lamivudine alone and in combination with other antiretroviral (ARV) drugs has been studied in HIV-infected children, and extensive data demonstrate that lamivudine appears safe and is associated with clinical improvement and virologic response[2-17]. Lamivudine is commonly used in HIV-infected children as a component of a dual-NRTI backbone[3-4, 6-7, 11-12, 14, 16-17]. In one study, the NRTI background components of lamivudine/abacavir were superior to zidovudine/lamivudine or zidovudine/abacavir in long-term virologic efficacy[18]. Because of its safety profile and availability in a liquid formulation, lamivudine has been given to infants during the first 6 weeks of life[11]. Recently, weight-band dosing recommendations for lamivudine have been developed[19-20].

The standard adult dosage for lamivudine is 300 mg once daily, but few data are available regarding once-daily administration of lamivudine in children. The pharmacokinetics (PKs) of once-daily versus twice-daily dosing of lamivudine were evaluated in HIV-infected children 2 to 13 years of age in the PENTA-13 trial[2] and in children 3 to 36 months of age in the PENTA 15 trial[21]. Both trials were

crossover design with doses of lamivudine of 8 mg/kg/once daily or 4 mg/kg/twice daily. Area under the curve $(AUC)_{0\text{-}24}$ and clearance values were similar and most children maintained an undetectable plasma RNA value after the switch. A study of 41 children 3 to 12 years of age (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent $AUC_{0\text{-}24}$ and good clinical outcome (disease stage and CD4 cell count) after a switch to once-daily lamivudine, with median follow-up of 1.15 years[22]. All three studies enrolled only patients who had low viral load or were "clinically stable" on twice-daily lamivudine before changing to once-daily dosing (see table below). There are no clinical trials of combination therapy with once-daily dosing of lamivudine in children. Therefore, the Panel supports consideration of switching to once-daily dosing of lamivudine in clinically stable patients with undetectable viral load and stable CD4 cell count, at a dose of 8 to 10 mg/kg/dose to a maximum of 300 mg once daily. More long-term clinical trials with viral efficacy endpoints are needed to confirm that once-daily dosing of lamivudine can be used effectively to initiate antiretroviral therapy (ART) in children.

Table: Steady-State Pharmacokinetics of Once- or Twice-Daily Lamivudine*

Study/(reference)	PENTA 15[21]		PENTA 13[2]		Arrow[22]	
Location	Europe		Europe		Uganda	
N	17		14		35	
Age (years)	2		5		7	
Sex (% male)	56%		43%		42%	
Race (% black or African American)	78%		Not Reported		100%	
Body weight (kg)	11		19		19	
Concurrent PI use	8		1		0	
Dosing interval (hours)	12	24	12	24	12	24
Administered dose (mg/kg)	4.04	8.02	4.05	8.1	4.7	9.6
$AUC_{0\text{-}24}$ (mg*hr/L)	9.48[a]	8.66[a]	8.88[a]	9.80[a]	11.97[a]	12.99[a]
C_{max} (mg/L)	1.05[a]	1.87[a]	1.11[a]	2.09[a]	1.80[a]	3.17[a]
C_{min} (mg/L)	0.08[a]	0.05[a]	0.067[a]	0.056[a]	0.08[a]	0.05[a]
Cl/F/kg (L/hr/kg)	0.79[a]	0.86[a]	0.90[a]	0.80[a]	0.79[a]	0.72[a]

** Data are medians except as noted*

[a] geometric mean

Lamivudine undergoes intracellular metabolism to its active form, lamivudine triphosphate. In adolescents, the mean half-life of intracellular lamivudine triphosphate (17.7 hours) is considerably longer than that of unmetabolized lamivudine in plasma (1.5–2 hours). Intracellular concentrations of lamivudine triphosphate have been shown to be equivalent with once- and twice-daily dosing in adults and adolescents, supporting a recommendation for once-daily lamivudine dosing in adolescents age 16 years and older who weigh 50 kg or more[23, 24].

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